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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,754	02/06/2004	Gerald Koelsch	022266-000930US	5585

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EXAMINER	
NOAKES, SUZANNE MARIE.	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/773,754	KOELSCH ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Status of the Application

2. Applicants amendments to the claims, abstract, specification and drawing are acknowledged. Claims 1-6 are pending and under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 23 October 2006 has been considered by the examiner. The majority of the references can be found in the abandoned divisional application 09/603,217. See signed and attached PTO-1449.

Withdrawal of Rejections/Objections

4. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement:

6. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibitors OM-99-1 and OM-99-2 (SEQ ID No: 27 and 28, respectively), does not reasonably provide enablement for any inhibitor that interact with the crystal of memapsin 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The instant claims are drawn to a method of treating a patient or decreasing the likelihood of developing Alzheimer's by administering an inhibitor with a K_i of 10^{-7} M or one that can bind to a crystallized memapsin 2 proteins. A critical aspect of the claimed invention is the necessary reproducibility of the crystallization conditions and making the co-crystal memapsin-2:SEQ ID No: 28 so that a skilled artisan can make and use the invention as claimed. However, in the absence of the actual exact protein content used to make the crystals and absence the actual structural coordinates used to model inhibitors, the instant claims would require undue experimentation by a skilled artisan in order to determine any inhibitors other than OM-99-2 and OM-99-1 that might be useful in the treatment of Alzheimer's and those which meet the limitations of the claims. The full details of the rejection can be found in the previous Office action in Section 14.

7. Claims 4-6 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering an effective amount of an inhibitor of memapsin 2 with a particular K_i or which binds to crystallized memapsin 2 with the parameters of Table 2 (claim 1), wherein the inhibitor is modeled using a computer program based on the three-dimensional structural coordinates of memapsin 2 (claim 4) and specifically those found in Table 2 (claims 5 and 6). However, Table 2 is merely a table which possesses X-ray data collection statistics and no structural information is present in said Table or the rest of the instant application. As such a skilled artisan would not be able to graphically display the memapsin 2 structure let alone model any inhibitors based on its structure without the burden of undue experimentation. The full details of the rejection can be found in the previous Office action in Section 15.

Written Description:

8. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The details of the rejection can be found in the previous Office action in Section 16.

9. Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The details of the rejection can be found in the previous Office action in Section 17.

Response to Arguments

10. Applicant's arguments filed 30 October 2006 have been fully considered but they are not persuasive.

Applicants have summarily argued that the claims do meet the standards for written description and enablement without addressing each individual rejection (there are four separate 35 U.S.C. 112 1st paragraph rejections as stated in the previous Office action and restated above). Applicants attempt to establish that the claims are enabled and that Applicants do have possession of the claimed invention by pointing to paragraphs [0018], [0019], [0020] and [0053-0055] of the specification and describing what each paragraph states. Paragraph 18 describes methods that have been developed for purification of catalytically active recombinant memapsin 2, paragraph 19 explains that the substrate subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate and the processes for synthesis of two inhibitors found this way e.g. OM-99-1 and OM-99-2 and that the inhibitor complex of OM-99-2 and memapsin was used to crystallize mempasin. Paragraph 20 states that this crystallographic information can be used to perform *in silico* design of other inhibitors. Finally paragraphs 53-55 describes in detail the synthesis of inhibitors of memapsin 2, including a description of five human aspartic proteases. This, however, is

not considered adequate arguments to overcome *any* of the 35 U.S.C. 112 1st paragraph rejections. As stated in the previous Office action, one skilled in the art has no clue what memapsin protein was used to co-crystallize OM-99-2:memapsin 2. Was it the full length? Specific domains? A truncated version? None of this disclosed in the specification and Applicants have not addressed these concerns so it is assumed that silence is concurrence with this assessment because the courts generally accepts as fact that which is not disputed by applicant. See *In re Kunzmann*, 140 USPQ 235 (CCPA 1964). Furthermore, Applicants have disclosed only two species of a rather broad genus of inhibitors, that being OM-99-1 and OM-99-2 each of which are eight amino acid peptides. These species are not deemed representative of the overall genus because there are thousands of organic molecules that are not peptidic in nature which could bind to the crystallized memapsin-2 protein. Thus, the two disclosed species are not representative of the entire genus. Even if the claims were limited to peptidic inhibitors, these two inhibitors still would not be sufficient to represent the overall genus because there are thousands of small peptides which could feasibly bind to the crystal, especially since the claims do not limit the binding to any particular active or binding site. Finally, there is no structure-function correlation between the claimed inhibitors which have K_i's of 10^{-7}. MPEP § 2163 states that if a biomolecule is described only by a functional characteristic, in this case a K_i value, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.".

The lack of enablement exists for the following reasons. Because a skill artisan does not know how to reproduce the protein crystals and because of the extensive unpredictability in the art of protein crystallography, then undue experimentation would be expected for a skilled artisan to design *de novo* crystallization experiments to see if specific inhibitors might bind to the co-crystal or not. Furthermore, Applicants have also failed to address the lack of any three-dimensional structural coordinates which would be used to perform *in silico* design or creating a data base of said designed inhibitors. Table 2 as stated previously is merely data collection and data refinement statistics and in no way is useful for performing *in silico* analysis and/or design. The actual three-dimensional structural coordinates are required but are absent from the instant application and at the very least for claims 4-6 there is no way to practice the claimed invention whatsoever without the structural coordinates.

Thus in summary, because a skilled artisan can not reproduce the crystals used in the claimed invention to identify inhibitors to which they bind then a skilled artisan has no hope or chance of creating any inhibitors that may meet the entire scope of each claim. Furthermore, because Applicant's also have not disclosed essential subject matter needed to practice the inventions, e.g. any three-dimensional structural coordinates, and because a skilled artisan could not even if they wanted to solve the crystal structure themselves (which is considered undue experimentation) because of reasons mentioned in the preceding sentence, then it is deemed that Applicants did not have possession of the invention at the time of filing nor is the specification enabling to

one skilled in the art to make or use the invention. As stated *supra*, Applicants silence on these points is considered admittance of the facts.

11. Applicant's arguments with respect to the rejection of claims 1 and 3 under 35 U.S.C. 102(a) have been fully considered and are persuasive. The rejection has been withdrawn.

Conclusion

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
04 January 2007

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER